

Inventor: PICKFORD ET AL
Serial No.: 10/501,538
Filing Date: 7/16/2004
Examiner: Christopher D. Prone
Group Art Unit: 3738

REMARKS

In response to the "Notice of Non-Compliant Amendment (37 CFR 1.121) the present paper comprises an **"entire corrected amendment."** In the present paper, amendments to claims 22, 28 and 34 have been properly underlined.

Claims 20-43 are present in the application. Claims 22, 28 and 34 have been amended to include a limitation for the concentration of silver. Method claims 41-43 are presented in view of the Examiner's kind suggestion.

As presented in the previous submission, the claims are characterized by the following features:

"An implant for use in a surgical procedure, said implant comprising a metal substrate and a surface layer integral with said metal substrate, said surface layer comprising an anodized layer grown from the metal of said metal substrate by anodizing, said surface layer incorporating a biocidal metal in an ionic form...

the biocidal metal ions being absorbed into said surface layer by ion exchange, and **the quantity of biocidal metal ions being such that the biocidal material is effective in suppressing infection after the surgical procedure.**"

The Examiner has rejected the claims under 35 U.S.C. 102 and 103 in view of U.S. Patent 5,185,075 (Rosenberg et al.) Rosenberg describes a process for anodizing a titanium implant using a phosphoric acid solution (primarily non-aqueous), and in

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which a small amount of silver nitrate solution may be added to precipitate any halides (which have a detrimental effect on the anodizing). The Examiner has now stated that: "The applicant argues that there is a large difference in the concentrations of silver ions absorbed between the current application and the Rosenberg patent. However this is not convincing because the claimed materials are still provided in the Rosenberg reference, which would then inherently have the same effects as that in the current application."

The Rosenberg reference does indeed mention anodizing, phosphoric acid, and silver nitrate. But, the overall process is a completely different process to that of the present invention; thus, the end product is significantly and necessarily structurally different. It differs in the manner in which the anodizing is carried out, and so in the nature of the resulting anodized surface; and it differs in the way in which silver nitrate is provided, and so in the concentration of silver ions in the resulting product. The differences are so significant that Rosenberg's implants would have no biocidal properties whatsoever, whereas the implants of the present invention have a significant and substantial biocidal property.

Considering first the anodizing process, Rosenberg carries out anodizing in such a way as to generate a dielectric film of titanium dioxide with high dielectric strength and with a high breakdown potential (column 3, lines 16-25), this requiring use of a substantially non-aqueous organic solvent for the phosphoric acid (column 3, lines 37-39). That is to say the anodizing is carried out in such a way as to ensure a good quality oxide layer is formed. The process typically involves a comparatively high voltage (the examples are from 100 to 500 V), and there is no point in going beyond the stage at which "age down" ends, beyond

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which the oxide film no longer becomes more resistive; subsequently the film integrity is attacked (column 7, lines 43-49). The resulting oxide layer is a good quality dielectric film, primarily consisting of titanium dioxide, without significant porosity or ion exchange properties.

The present invention, by contrast, carries out anodizing with an aqueous electrolyte, in such a way as to form a surface coating of titanium phosphate and/or titanium oxide which has significant ion exchange properties. The surface coating must have a degree of porosity, as a smooth surface cannot absorb sufficient silver. (If silver ions were to be absorbed as a monolayer onto a smooth surface, over the entire surface, the absorption would be about $0.3 \mu\text{g}/\text{cm}^2$; in contrast the silver level measured in the present invention is $73 \mu\text{g}/\text{cm}^2$.)

As explained in the previous submission, i.e., in the Amendment filed on December 18, 2006, in Rosenberg's process a small amount of silver nitrate may be added to the phosphoric acid, to ensure that any halides are precipitated; sufficient silver nitrate may be added that (yellow) silver phosphate is precipitated. But, it will be appreciated by those having ordinary skill in this art that the particles of silver halide and silver phosphate that precipitate are not part of the surface oxide layer. Furthermore, the concentration of silver ions in solution must be very low, because silver phosphate is substantially insoluble. Since the solution is acidic, any hypothetical ion exchange of silver ions with the titanium dioxide is suppressed by the much greater concentration of hydrogen ions.

In contrast, in the process of the present invention, after anodizing, the implant is rinsed; only then is it contacted with an aqueous solution of 0.1 M silver nitrate. So, the ion ex-

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change takes place using a liquid in which the silver ion concentration is about 1,000,000 times greater than the hydrogen ion concentration (pH7 means the hydrogen ion concentration is 10^{-7} M = 0.1 μ M). Hence, the ion exchange process - considering only the difference in the solutions - is about 500,000,000 times more effective in the present invention than in the Rosenberg process.

Taking both these considerations into account, the amount of silver that can be absorbed by ion exchange into an implant of the present invention, as compared to one treated by Rosenberg's process, will be considerably greater than 500,000,000 times greater!

U.S. Patent 6,113,636 (Ogle) points out that: "Healthy humans generally have for example plasma levels of Ag of about 0.2 μ g/L to about 10 μ g/L, where 10 μ g/L corresponds to about 10 ppb ... Serum silver ion concentrations of about 300 ppb have been associated with toxic symptoms ... Silver ion concentrations of about 4 mg/L [= 4000 μ g/L] are known to cause rapid cell death. Therefore, it is preferable to keep silver ... ion concentrations in the bloodstream safely below toxic levels and preferably below levels where any symptoms are observable." (Column 5, lines 10-13 and 21-28).

That information would appear to be objective and uncontentious, at least as regards the broad picture. For an implant to have any biocidal properties, it clearly must contain sufficient silver ions to raise the levels of Ag significantly above those ordinarily present. But, the range between the lowest normal level in a healthy human (0.2 μ g/L) and concentrations that could be fatal (say 4000 μ g/L) differ by only a factor of 20,000. The implants of the present invention do have such a biocidal effect.

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Assuming that the implants of the present invention generate a silver ion concentration in the plasma of say 100 µg/L, then the corresponding silver ion concentration provided by Rosenberg's procedure (taking only the difference in the solutions into account) would be less than 0.2 µg/L, that is to say about a million times less than the lowest normal level in human plasma, and so clearly having no significant effect.

It is thus clear that Rosenberg's procedure produces an implant with a much less porous oxide surface, with markedly less ion exchange properties; and that the extent to which silver is absorbed by ion exchange is completely insignificant and negligible. Such an implant would produce no change in the level of biocidal ions already present in the patient! And so it "inherently" does not have the effect of the present invention, as claimed.

By contrast, the present invention provides an implant with a significantly more porous oxide surface, with considerably greater ion exchange properties; and silver is absorbed by ion exchange by a far more effective procedure, leading to an enormously greater loading of silver. Hence, the implants of the present invention have a significant biocidal effect.

Accordingly, applicants submit that the present claims clearly distinguish from Rosenberg et al. in "the quantity of biocidal metal ions being such that the biocidal material is effective in suppressing infection after the surgical procedure" as recited in parent claims 20, 26 and 32. Accordingly, applicant's believe that that claims 20-40 are directed to allowable subject matter and such action by the Examiner is courteously solicited.

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The Rosenberg implants are structurally different:

-Rosenberg's implants provide good quality oxide layers with "minimum leakage current" < 25 microamps/cm² as compared with our oxide layers which are ion absorbing (and consequently have much larger leakage currents).

-Rosenberg's implants contain immeasurably small quantities of Ag (over 1,300,000 times less than our value).

-Rosenberg's implants have no effect in suppressing infection.

The examiner has suggested that the Rosenberg implants would "inherently have the same effect," and has objected that we have not defined any effective ranges. This is incorrect. For the implant to have the required effect of suppressing infection, it inherently must change the level of the biocidal ions (Ag ions) in the patient, without exceeding the level at which toxic effects occur. Since it is known that human body fluids naturally contain Ag ions at a low level (say around 10 ppb), and that this natural low level does not have the effect of suppressing infection, there is an inherent requirement that the implants must have a significant impact on the level of Ag ions in the body fluids adjacent to the implant. The implants of the present invention provide exactly this effect. But, they also must not raise the Ag ion level to toxic values, which are around 300 ppb. And, if the quantity of silver in the implant is immeasurably small (as in Rosenberg's case), then it will not have any effect in suppressing infection.

The calculations of the Ag concentrations in Rosenberg's case have been reconsidered and reassessed by applicants. The calculations had previously been based on the known figure for the

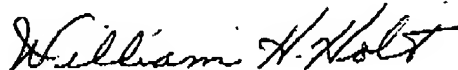
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very low solubility of silver phosphate, but, because of the complexities arising from the use of the organic solvent and the possibility that the acidity may also affect the solubility, the calculation has instead been based on Rosenberg's stated intention to add only sufficient silver nitrate to precipitate any chloride; and the calculation has then assumed (choosing a worst case scenario) that 10 times this quantity of silver nitrate was added. The fact remains that Rosenberg's solution is well over 1.3 million times less effective for achieving Ag ion absorption.

Favorable action on the merits is courteously solicited.

Respectfully submitted,

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